REMARKS

Claims 1-40 were presented in the original application. Claims 1-6, 8-12, 14-17, 19, 21-26, and 31-40 were previously pending. The Office withdrew claims 2-4, 14-17, 19, 21-25, and 33-40 pursuant to making the Restriction Final in the Office Action of November 27, 2009 (hereinafter referred to as "the Office Action"). Applicant has amended claims 1, 2, 4, 9, 10, 11, 21, 26, 31, 32, and 34-40 and canceled claims 3, 5, 6, 8, 12, 14-17, 19-20, 22-25, and 33 herewith.

DRAWINGS

Applicant provides herewith a set of replacement drawings for Figures 5, 6, and 7 under 37 CFR §1.121(d) as per the Office's request. The replacement drawings for Figures 5, 6, and 7 provided herewith correspond respectively to the replacement sheets for drawing sheets 6/54, 7/54, and 8/54 as originally filed. The only changes to said drawing sheets as originally filed are the substitution of a clear reproduction of the photographs (Figures 5 and Figure 6) or line drawings (Figure 7). Applicant hereby states that no new matter has been introduced in the replacement drawings.

SPECIFICATION

As requested by the Office, Applicant has corrected one typographical error that they have become aware of in the amendment to the specification filed herewith. The Office is respectfully alerted to the requested amendment in the third to last sentence of this paragraph where an empty set of parentheses are deleted.

ELECTION/RESTRICTIONS

In the Office Action dated November 27, 2009, the Office made Final the Restriction. As the Applicant has made their election with traverse and requested reconsideration of the Restriction, Applicant is entitled to petition the Director to review the Restriction under 37 CFR §1.144. As any withdrawn claims are subject to reinstatement in the event that the Restriction is withdrawn or overruled by the Director under 37 CFR §1.144, Applicant has amended certain

withdrawn claims herewith to preserve their potential right to have such claims examined. The absence of counterarguments in this Response to the reasons for making the Restriction final advanced by the Office in the Office Action should not be construed as any admission by the Applicant that the Restriction is proper or warranted.

REJECTIONS OF CLAIMS UNDER 35 USC §112, 1st PARAGRAPH:
WRITTEN DESCRIPTION

In the Office Action, previously pending claims 1, 5-6, 8-10, 26, and 31-32 were rejected under 35 USC §112, 1st paragraph, as allegedly failing to meet the written description requirement. The Office alleged that the specification failed to demonstrate that the Applicant was in possession of either: i) the genus of regulators capable non-expression of a regulatory protein in vivo causes synthesis of a first antigen that is conserved among Salmonella species and Escherichia coli (E. coli); or ii) the genus of regulators capable a means of regulating synthesis for a first carbohydrate, wherein said first carbohydrate antigen ceases to be synthesized in vivo, and exposing a second carbohydrate antigen. The Office Action further alleges iii) that the specification fails to disclose how to determine what constitutes first carbohydrate antigen capable of ceasing synthesis in vivo and exposing a second carbohydrate antigen and therefore lacks written description of the instant claimed invention.

With respect to item i) (i.e. "the genus of regulators capable non-expression of a regulatory protein in vivo"), Applicant respectfully notes that the claims as currently amended are drawn to "a regulatable *araC*P_{BAD} promotor that is operably linked to a *fur* gene". As such, the Office's rejections of the claims as not teaching "any structural limitations of any regulators" (page 7 of the Office Action) are obviated with respect to item i) as the claims as currently amended recite a specific promotor. This specific *araC*P_{BAD} promoter was known at the time of filing, structurally defined, and shown to function as per the claims in working examples provided by the Applicant. There is thus no reason to believe that one of ordinary skill in the art would doubt that the Applicant was in possession of the *araC*P_{BAD} promoter.

With respect to item ii) (i.e. "the genus of regulators capable a means of regulating synthesis for a first carbohydrate"), Applicant points to the disclosure of the specification on pages 18, 19, and 20 of the Application as filed that disclose regulators of LPS-O antigens and

the claim amendments presented herewith that substitute "an LPS-O antigens" for "a first carbohydrate". More specifically, the specification discloses both mutations in or regulation of genes of the *rfb* gene cluster as well as mutations in the *pmi* gene that are suitable for regulating expression of LPS O-antigens. On page 20, the specification further indicates that such regulation can be achieved by replacing a promoter for any of the *rfb* genes that are needed for synthesis of the LPS O-antigen with the *araC*P_{BAD} activator-repressor-promoter system. There is thus no reason to believe that one of ordinary skill in the art would doubt that the Applicant was in possession of various means for regulating synthesis of LPS O-antigens as currently claimed.

With respect to item iii) (i.e. that the specification fails to disclose how to determine what constitutes first carbohydrate antigen capable of ceasing synthesis in vivo and exposing a second carbohydrate antigen), Applicant first notes that the claims as currently amended recite: a) "an LPS O-antigen" rather than "a first carbohydrate antigen" and "exposing an LPS core oligosaccharide antigen" rather than "a second carbohydrate antigen". At the time of filing, those skilled in the art would recognize what constitutes "an LPS-O antigen" and what constitutes "an LPS core oligosaccharide". For example, the discussion of these bacterial antigens spanning pages 2 and 3 of the specification as originally filed amply demonstrates that those skilled in the art would recognize the identity of these elements of the claims as currently amended.

In view of these considerations, Applicant respectfully requests that the Examiner withdraw the rejections of the claims under 35 USC §112, first paragraph, for lack of written description.

REJECTIONS OF CLAIMS UNDER 35 USC §112, 1st PARAGRAPH: ENABLEMENT

In the Office Action, previously pending claims 1, 5-6, 8-10, 26, and 31-32 were rejected under 35 USC §112, 1st paragraph, as allegedly failing to meet the enablement requirement.

Considering the relevant *Wands* factors of claim breadth, Applicant first notes that the claims as currently amended are drawn to:

i) a regulatable *araC*P_{BAD} promotor that is operably linked to a *fur* gene rather than to a "means for regulatable expression of a *fur* gene";

ii) a means for regulating synthesis of an LPS O-antigen rather than to "a means for regulatable synthesis of any carbohydrate antigen"; and,

iii) exposing an LPS core oligosaccharide antigen rather than to "exposing any carbohydrate antigen". However, the Applicant has not limited the claims to the very specific *Salmonella* strains provided as exemplary embodiments in the specification as it would be well within the abilities of one skilled in the art to practice the invention as claimed with other *Salmonella* and *Escherichia coli* strains as both of these bacterial genera were exceptionally well characterized at the time of filing.

Considering the relevant *Wands* factors of guidance of the specification/existence of working examples, the Office argued that the specification was "devoid of any teaching that the claimed prevents *Salmonella* and *E.coli* infection" and that one skilled in the art "would not accept on its face the examples given in the specification as being correlative or representative of a successful model".

First, all of the claims under consideration by the Office are drawn to a "live attenuated strain of *Salmonella*". The Applicant demonstrates in Example 6 (see pages 40-41, see Table 7) that mice inoculated with an exemplary live attenuated strain (Δpmi-2426 ΔPfur223;;TT *araC* P_{BAD}) exhibit 80-100% survivorship following a challenge dose of virulent wild-type *Salmonella* that is two orders of magnitude (i.e. $1X10^9$) greater than the challenge dose of wild type virulent *Salmonella* (i.e. $1X10^7$) that results in 0% survivorship in control mice that are not inoculated with the exemplary live attenuated strain. The Applicant further demonstrates in Example 7 (see pages 41-42, see Table 8) that mice inoculated with an exemplary live attenuated strain exhibit a dose dependent increase of up to 80% survivorship following a challenge dose of a second and distinct virulent wild-type *Salmonella* that results in 0% survivorship in control mice that are not inoculated with the exemplary live attenuated strain. The Applicant also demonstrates in Example 8 (pages 42-43) and the associated figures 11 and 12 that mice inoculated with the exemplary live attenuated strain exhibit substantial antibody responses to the OMPs and IROMPs from a wide variety of *Salmonella* and *E.coli* strains. The observed antibody responses to IROMPs from a wide variety of *Salmonella* and *E.coli* strains is especially significant in that contemporaneous art teaches that antibodies directed against IROMPs can provide some degree of immuno-protection (see Bolin et al. Infect. Immun. 55(5), 1239, 1987, referred to by the Office on Page 12 of the response) and thus weighs in favor of enablement. Applicant therefore respectfully disagrees with the Office's statement that "(t)he working examples do not disclose

any empirical data or results indicative of a preventing *Salmonella* and *E.coli* infection as claimed".

Applicant also respectfully reminds the Office that it "must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example" and that "a rigorous or an invariable exact correlation is not required" (see MPEP §2164.02, citing Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)). Although the Office states that "the data fails to show...vaccine protection", the Examples cited above appear to show just that (i.e. that mice inoculated with the invention as claimed survive a *Salmonella* challenge whereas inoculated control mice perish following the *Salmonella* challenge). The Office is therefore respectfully requested to provide such reasons to support the alleged "lack of correlation" in the event that the Office maintains the rejections of claims for an alleged lack of enablement.

Furthermore, Applicant respectfully requests that the Office provide some basis for the allegation "that one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model" (page 12 of the Office Action). It is noted that experiments substantially similar in design to the aforementioned working examples provided by the applicant has both in the past and currently been held by those skilled in the art to provide evidence of protective immunity. More specifically, the Office is respectfully directed to the publication in a peer reviewed scientific journal in 1987 (see Curtiss and Kelly, Infect. Immun. 55(12):3035, 1987, provided herewith in an accompanying IDS) where substantially similar experiments are used to demonstrate the effectiveness of oral immunization with avirulent Salmonella (see Table 7, pg. 3041 and related paragraph on pg. 3040). The Office is also respectfully directed to a more recent 2009 publication in that same peer reviewed scientific journal (see Curtiss et al, Infect. Immun. 77(3):1071, 2009, provided herewith in an accompanying IDS) where substantially similar experiments are used to demonstrate induction of protective immunity with attenuated *Salmonella* strains (see Table 7, pg. 3041 and related paragraph on pg. 3040). Based on these two publications in a peer reviewed scientific journal, it is evident that those skilled in the art in fact accepted the types of experiments presented by the Applicant as being correlative both in 1987 and in 2009. Applicant further notes that the Office

also relies on an article published in 1987 in this same peer reviewed scientific journal as being representative of the "state of the art" (see Bolin et al. Infection and Immunity 1987 reference cited by the Office on Page 12 of the Office Action).

With respect to the state of the art, Applicant notes that it is important to consider pertinent differences between what is disclosed in the various publications cited by the Office and the invention as claimed. It is also important to recognize where the state of the art is such that it supports enablement. Thus, both Bolin et al. (Infect. Immun. 55(5), 1239, 1987) and Sood et al. (Mol Cell Biochem. 273(1-2):69, 2005) disclose passive immunization of subjects with an antibody raised against IROMPs whereas the Applicant's invention is directed to live attenuated strains of *Salmonella* that induce production of antibodies in an inoculated host organism. Sood et al. additionally disclose in the Abstract of their publication that mice that were actively immunized with IROMPs were protected against challenge by the pathogen. One skilled in the art would expect a much more robust immuno-protection would be obtained in a host inoculated with a live attenuated strain that can elicit a sustained host immune response than would be obtained in a host passively immunized with an antibody that would eventually be cleared from the host. Even in spite of this very critical difference between the Applicant's live attenuated strains and the experiments described in the cited references, that both Bolin et al. and Sood et al. in fact observed a certain level of protection by passive immunization with antibodies against IROMPs thus indicates that IROMPs are effective antigens for inducing some level of protective immunity against *Salmonella,* indicating that the pending claims were enabled.

The Office then describes various publications that indicate that an antigen's ability to stimulate antibody production does not *necessarily* correlate with an ability to an immune response capable of protecting an animal against infection (US 6,248,329 and Ellis, both cited on Page 12 of the Office Action). However, the Bolin et al. and Sood et al. references provided by the Office indicate that IROMPs apparently fall in that subset of antigens that do result in a certain level of a protective response to infection, again indicating that the pending claims were enabled.

The Office also cites the Greenspan et al. reference (Nature Biotechnology 17 (10):936, 1999) that speak to the difficulty of defining immuno-epitopes and argues that immuno-epitopes that elicit a protective immuno-response can only be identified empirically. Again, the

difficulties referred to in Greenspan et al. and by the Office are pertinent to compositions (i.e. protein epitopes) that are very different than the live attenuated strains provided by the Applicant that present a variety of outer membrane proteins (including LPS core oligosaccharide antigen and IROMPs) on their surface in an intact form where all accessible epitopes of those proteins are present. The Applicant's compositions thus do not rely on nor require identification of a single epitope of a single antigen as described in Greenspan et al. to elicit a protective response but rather present a series of antigens (including LPS core oligosaccharide antigen and IROMPs) in a form where multiple epitopes of each of those antigens are presented. Consequently, whatever unpredictability is associated with immunogenic protein epitope compositions of Greenspan et al. is not relevant to the live attenuated strains as claimed by the Applicant that do not rely on epitope predictions or use of a single epitope. As pointed out previously, the state of the art was such that there was an indication that one of the antigens (i.e. IROMPs) presented by the live attenuated derivatives can in and of itself provide a certain level of protective immunity, indicating that the pending claims were enabled. Furthermore, in the Applicant's case, there are working examples that demonstrate that the live attenuated strains as claimed actually provide protection to mice challenged with virulent *Salmonella.*

In view of these considerations, the Applicant respectfully requests that the Examiner withdraw the rejections of the claims under 35 USC §112, first paragraph, for lack of enablement.

REJECTIONS OF CLAIMS UNDER 35 USC §112, 2nd PARAGRAPH: INDEFINITENESS

The Office rejected as indefinite independent claim 1 for use of the phrase "means for regulatable" as rendering it impossible to determine the equivalents of the "means" element under 35 USC §112, six paragraph , citing *Ex parte Klumb*, 159 USPQ 694 (Bd. App. 1967). Applicant has addressed this rejection by amending claim 1 to recite "means for regulating". The Office is referred to both MPEP §706.03(d) and MPEP §2181 as supporting "means for" claims constructions where the function either precedes or follows "means for". More specifically MPEP §2181 states: "B) "printing means" and "means for printing" which would have the same connotations. Ex parte Klumb, 159 USPQ 694 (Bd. App. 1967)."

The rejections of claim 1 as indefinite for use of the phrases "first antigen", "first carbohydrate antigen", and "second carbohydrate antigen" are rendered moot by the deletion of those phrases from claim 1 as currently amended.

The Office further alleged that use of the term "ceases" in claim 1 rendered that claim indefinite by failing to deine the metes and bounds of the invention. Applicant respectfully requests that the Office reconsider this rejection as: i) the term "cease' has a plain dictionary meaning (i.e. "to cause to come to an end especially gradually" in the Merriam-Webster Online dictionary available on the internet at www.merriam-webster.com/dictionary) that is no more or less definite than the substitute term "inhibits" (i.e. "to hold in check : restrain" in the Merriam-Webster Online dictionary available on the internet at www.merriam-webster.com/dictionary) that was proposed by the Office; ii) the term ceases is used throughout the specification to describe the reduction in LPS O-side chains that occurs as a function of time or numbers of generations of growth in the live attenuated strains of the invention; and iii) an examination of Figure 5 shows that the term ceases is entirely appropriate to describe the gradual reduction in LPS O-antigen that is observed in the live attenuated strains as claimed. Applicant thus believes that one of skill in the art would be advised of the metes and bounds of the claim by virtue of dictionary definitions of the term "ceases", its use throughout the specification, and the experimental data presented in figure 5 that illustrates the time course by which the presence of LPS O-antigens diminishes.

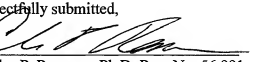
CONCLUSION

Applicant believes that a complete response to the Office Action of November 27, 2009 is provided herewith and respectfully request that the Office reconsider and withdraw the rejections of the claims in light of the amendments and remarks provided herein.

It is not believed that extensions of time are required beyond those which may otherwise be provided for in this filing. In the event however that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. §1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account 20-0823.

The Examiner is encouraged to contact the undersigned via telephone at the number provided, if it is determined that personal communication will expedite prosecution of this application.

Respectfully submitted,



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